REMARKS

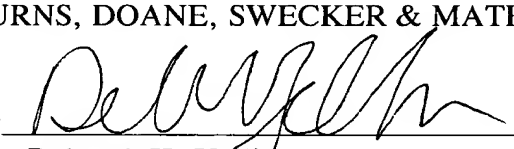
This Second Supplemental Preliminary Amendment is supplementary to the Supplemental Preliminary Amendment filed on December 28, 2001. The Supplemental Preliminary Amendment provided a complete substitute Sequence Listing in timely response to an Office Communication mailed November 28, 2001 (Paper No. 5).

The present Second Supplemental Preliminary Amendment sets forth all amendments to the specification and the claims which became necessary as a result of the substitute Sequence Listing, *i.e.*, the proper Sequence identifiers have been placed in the application.

Favorable consideration on the merits is respectfully requested.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By 

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Paragraph beginning at Page 7, line 34 and ending on Page 8, line 3

--The fragment in said process may be a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain. In preferred embodiments said fragment is a peptide comprising the amino acid sequence (SEQ ID No.: 7) [KLGFFAHKKIPEEEKREEKLEQ,] or a fragment comprising the amino acid sequence from about amino acid No. 952 to about amino acid No. 986 of SEQ ID No. 2 [1], or a fragment comprising the amino acid sequence from about amino acid No. 140 to about amino acid no. 337 of SEQ ID No. 2 [1].--

Paragraph beginning at Page 8, line 7

--The process may also be used for detecting the presence of an integrin subunit $\alpha 10$ comprising the amino acid sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4 [2], or of an integrin heterodimer comprising said subunit $\alpha 10$ and a subunit β, or of homologues or fragments thereof having similar biological activity.--

Paragraph beginning on Page 8, line 33

In a still further embodiment this process is a process for detecting the presence of an integrin subunit $\alpha 10$, or of a homologue or fragment of said integrin subunit having similar biological activity, on cells, whereby a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide chosen from the nucleotide sequence shown in SEQ ID No. 1 is used as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit $\alpha 1$. Said cells may be chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts. Said integrin fragment may be a peptide chosen from the group comprising peptides of the cytoplasmic domain, the I-domain and the spliced domain, such as a peptide comprising the amino acid sequence (SEQ ID No.:7) [KLGFFAHKKIPEEEKREEKLEQ], or a fragment comprising the amino acid sequence from about amino acid no. 952-to about amino acid

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no. 986 of SEQ ID No. 2 [1], or a fragment comprising the amino acid sequence from about amino acid No. 140 to about amino acid no. 337 of SEQ ID No. 2 [1].

Paragraph beginning on Page 9, line 27

--The invention also relates to a process for determining the differentiation-state of cells during development, in pathological conditions, in tissue regeneration and in therapeutic and physiological reparation of cartilage, whereby a polynucleotide or oligonucleotide chosen from the nucleotide sequence shown in SEQ ID No. 1 is used as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit α1. Embodiments of this aspect comprise a process, whereby said polynucleotide or oligonucleotide is a polynucleotide or oligonucleotide coding for a peptide chosen from the group comprising peptides o-f the cytoplasmic domain, the I-domain and the spliced domain, such as a polynucleotide or oligonucleotide coding for a peptide comprising the amino acid sequence (SEQ ID No.: 7) [KLGFFAHKKIPEEEKREEKLEQ], or comprising the amino acid sequence from about amino acid No. 952 to about amino acid no. 986 of SEQ ID No. 1, or the amino acid sequence from about amino acid No. 140 to about amino acid No. 337 of SEQ ID No. 1. Said pathological conditions may be any pathological conditions involving the integrin subunit α10, such as rheumatoid arthritis, osteoarthrosis or cancer, or atherosclerosis or inflammation. Said cells may be chosen from the group comprising chondrocytes, smooth muscle cells, endothelial cells, osteoblasts and fibroblasts.--

Paragraph beginning on Page 14, line 34 and ending on Page 15, line 22

--The deduced amino acid sequence of α10 was found to share the general structure of the integrin a subunits described in previously published reports (6-21). The large extracellular N-terminal part of α10 contains a seven-fold repeated sequence which was recently predicted to fold into a β-propeller domain (32). The integrin subunit α10 contains three putative divalent cation-binding sites (DxD/NxD/NxxxD) (53), a single spanning

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transmembrane domain and a short cytoplasmic domain. In contrast to most a-integrin subunits the cytoplasmic domain of α10 does not contain the conserved sequence KXGFF (R/K) R. The predicted amino acid sequence in α10 is KLGFFAH. Several reports indicate that the integrin cytoplasmic domains are crucial in signal transduction (54) and that membrane-proximal regions of both α- and β-integrin cytoplasmic domains are involved in modulating conformation and affinity state of integrins (55-57). It is suggested that the GFFKR motif in α-chains are important for association of integrin subunits and for transport of the integrin to the plasma membrane (58) . The KXGFFKR domain has been shown to interact with the intracellular protein calreticulin (59) and interestingly, calreticulin-null embryonic stem cells are deficient in integrin-mediated cell adhesion (60) . It is therefor possible that the sequence (SEQ ID No.:9) [KLGFFAH] in α10 have a key function in regulating the affinity between α10β1 and matrix proteins.--

Paragraph beginning on Page 18, line 33 and ending on Page 19, line 13

--The degenerate primers (SEQ ID No.: 9) [GAY AAY ACI GCI CAR AC] ((SEQ ID No.: 10) [DNTAQT], forward) and (SEQ ID No.: 11) [TIA TIS WRT GRT GIG GYT] ((SEQ ID No.: 12) [EPHHSI] reverse) were used in PCR (Camper et al, JBC, 273, 2038320389 (1998) to amplify the nucleotide sequence corresponding to the bovine peptide 1 (Figure 2) . A 900 bp PCR-fragment was then amplified from bovine, cDNA using an internal specific primer (SEQ ID No.: 13) [TCA GCC TAC ATT CAG TAT] (SEQ ID No.: 14) [SAYIQY], forward) corresponding to the cloned nucleotide sequence of peptide 1 together with the degenerate primer (SEQ ID No.:15) [ICK RTC CCA RTG ICC IGG] ((SEQ ID No.:16) PGHWDR, reverse) corresponding to the bovine peptide 2 (Figure2). Mixed bases were used in positions that were twofold degenerate and inosines were used in positions that are three- or fourfold degenerate. mRNA isolation and CDNA synthesis was done as earlier described (Camper et al, JBC, 273, 20383-20389 (1998)). The purified fragment was cloned, purified and sequenced as earlier described (Camper et al, JBC, 273, 20383-20389 (1998)).--

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Paragraph beginning on Page 19, line 28 and ending on Page 20, line 8

--The cloned 900bp PCR-fragment, corresponding to bovine α10-integrin, was digoxigenin-labelled according to the DIG DNA label-ling kit (Boehringer Mannheim) and used as a probe for screening of a human articular chondrocyte λZapII cDNA library (provided by Michael Bayliss, The Royal Veterinary Basic Sciences, London, UK) (52) . Positive clones containing the pbluescript SK+ plasmid with the cDNA insert were rescued from the ZAP vector by *in vivo* excision as described in the ZAP-cDNA® synthesis kit (Stratagene) . Selected plasmids were purified and sequenced as described earlier (Camper et al, JBC, 273, 20383-20389 (1998)) using T3, T7 and internal specific primers. To obtain CDNA that encoded the 5' end of α10 we designed the primer (SEQ ID No.:17) [AAC TCG TCT TCC AGT GCC ATT CGT GGG] (reverse; residue 1254-1280 in α10 CDNA) and used it. for rapid amplification of the CDNA 5' end (RACE) as described in the Marathon™ cDNA Amplification kit (Clontech INC., Palo Alto, CA).--

Paragraph beginning on Page 29, line 27 and ending on Page 30, line 9

--A plasmid for intracellular expression in E. coli of the alternatively spliced region (amino acid pos. 952-986, SEQ. ID 1) was constructed as described. The alternatively spliced region were back-translated using the E. coli high frequency codon table, creating a cDNA sequence of 96% identity with the original sequence (SEQ. ID 1 nucleotide pos 2940-3044). Using sequence overlap extension (Horton et al., Biotechniques 8:528, 1990) primer α10pfor (tab. I) and α10pfor (tab. I) was used to generate a double stranded fragment encoding the α10 amino acid sequence. This fragment was used as a PCR template with primers α10pfor2 (tab. I) and αl0prev2 (tab. I) in order to generate restriction enzyme site for sub-cloning in a pET vector containing the Z-domain of staphylococcal protein A, creating a fusion of the α10 spliced region with the amino terminal of the Z-domain with trombin cleavage site residing in-between. The fragment

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generated in the second PCR reaction is shown (SEQ ID No. 5 [3]) also indicating the unique restriction enzymes used for sub-cloning in the expression vector.--

Table I beginning on Page 30, line 12

α10pfor (SEQ ID No.: 18)	5'GTTCAGAACCTGGGTTGCTACGTTGTTTCCGGTCTGATC ATCTCCGCTCTGCTGCCGGCTGT-3'
α10pfor2 (SEQ ID No.: 19)	5'GGGGCATATGGTTCAGAACCTGGGTTGCTACGTTG-3'
α10prev (SEQ ID No.: 20)	5'GATAACCTGGGACAAGCTTAGGAAGTAGTTACCACCGT GAGCAACAG CCGGCAGCAGAGCGGA-3'
α10prev2 (SEQ ID No.: 21)	5'GGGGGGATCCGCGCGGCACCAGGCCGCTGATAACCTGG GACAAGCTTAGGAAGT-3'

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1. (Amended) A recombinant or isolated collagen binding integrin subunit α10 comprising essentially the amino acid sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4 [2], or homoloques or fragments thereof having essentially the same biological activity.

2. (Amended) A process of producing a recombinant integrin subunit α10 comprising essentially the amino acid sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4 [2] or homoloques or fragments thereof having essentially the same biological activity, which process comprises the steps of

a) isolating a polynucleotide comprising a nucleotide sequence coding for an integrin subunit α10, or homoloques or fragments thereof having essentially the same biological activity,

b) constructing an expression vector comprising the isolated polynucleotide,

c) transforming a host cell with said expression vector,

d) culturing said transformed host cell in a culture medium under conditions suitable for expression of integrin subunit α10, or homoloques or fragments thereof having essentially the same biological activity, in said transformed host cell, and, optionally,

e) isolating the integrin subunit α10, or homologues or fragments thereof having essentially the same biological activity, from said transformed host cell or said culture medium.

4. (Amended) An isolated polynucleotide comprising a nucleotide coding for an integrin subunit α10, or for homologues or fragments thereof having essentially the same

biological activity, which polynucleotide comprises essentially the nucleotide sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4 [2] or suitable parts thereof.

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6. (Amended) A vector comprising a polynucleotide or oligonucieotide coding for an integrin subunit α10, or for homologues or fragments thereof having essentially the same biological activity, which polynucleotide or oligonucleotide comprises essentially the nucleotide sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4 [2] parts thereof.

9. (Amended) A cell generated by steps a) to d) of the process as defined in claim 2, in which a polynucleotide or oligonucleotide coding for an integrin subunit α10, or for homologues or fragments thereof having essentially the same biological activity, which polynucleotide or oligonucleotide comprises the nucleotide sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4 [2] or parts thereof, has been stably integrated in the cell genome.

10. (Amended) Binding entities having the capability of binding specifically to an integrin subunit α10 comprising the amino acid sequence of SEQ ID No. 2 [1] or SEQ ID No. 4 [2], or to homologues or fragments thereof.

13. (Amended) A recombinant or isolated integrin heterodimer comprising a subunit α10 and a subunit β, in which the subunit α10 comprises essentially the amino acid sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4 [2], and homologues and fragments thereof having essentially the same biological activity.

15. (Amended) A process of producing a recombinant integrin heterodimer comprising a subunit α10 and a subunit β, in which the subunit α10 comprises essentially the amino acid sequence shown in SEQ ID No. 2 [1] and SEQ ID No. 4 [2], homoloques and fragments thereof having essentially the same biological activity, which process comprises the steps of

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a) isolating one polynucleotide comprising a nucleotide sequence coding for a subunit α10 of an integrin heterodimer and, optionally, another polynucleotide comprising a nucleotide sequence coding for a subunit β of an integrin heterodimer, or polynucleotides or oligonucleotides coding for homologues or fragments thereof having essentially the same biological activity,

b) constructing an expression vector comprising said isolated polynucleotide coding for said subunit α10 optionally in combination with an expression vector comprising said isolated nucleotide coding for said subunit β,

c) transforming a host cell with said expression vector or vectors,

d) culturing said transformed host cell in a culture medium under conditions suitable for expression of an integrin heterodimer comprising a subunit α10 and a subunit β, or homologues or fragments thereof having essentially the same biological activity, in said transformed host cell, and, optionally,

e) isolating the integrin heterodimer comprising a subunit α10 and a subunit β, or homologues or fragments thereof having essentially the same biological activity, or the α10 subunit thereof from said transformed host cell or said culture medium.

17. (Amended) A cell containing a first vector, said first vector comprising a polynucleotide or oligonucleotide coding for a subunit α10 of an integrin heterodimer, or for homologues or parts thereof having essentially the same biological activity, which polynucleotide or oligonucleotide comprises essentially the nucleotide sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4 [2] or parts thereof, and a second vector, said second vector comprising a polynucleotide or oligonucleotide coding for a subunit β of an integrin heterodimer, or for homologues or fragments thereof having essentially the same biological activity.

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23. (Amended) A fragment according to claim 22, which is a peptide comprising the amino acid sequence SEQ ID No. 7 [KLGFFAHKKIPEEEKREEKLEQ].

24. (Amended) A fragment according to claim 22, which comprises the amino acid sequence from about amino acid No. 952 to about amino acid no. 986 of SEQ ID No. 2 [1].

25. (Amended) A fragment according to claim 22, which is a peptide comprising the amino acid sequence from about amino acid No. 140 to about amino acid no. 337 of SEQ ID No. 2 [1].

31. (Amended) An *in vitro* process of using an integrin subunit α10 rising the amino acid sequence shown in SEQ ID No. 2 [1] SEQ ID No. 4 [2], or an integrin heterodimer comprising said subunit α10 and a subunit β, or a homologue or fragment of said integrin or subunit having essentially the same biologically activity, as a marker or target molecule of cells or tissues expressing said integrin subunit α10, which cells or tissues are of animal including human origin.

33. (Amended) An *in vitro* process according to claim 31, whereby said fragment is a peptide comprising the amino acid sequence SEQ ID No.: 7 [KLGFFAHKKIPEEEKREEKLEQ].

34. (Amended) An *in vitro* process according to claim 31, whereby said fragment comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of No. of SEQ ID no. 2[1].

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35. (Amended) An *in vitro* process according to claim 31, whereby said fragment comprises the amino acid sequence from about amino acid no. 140 to about amino acid no. 337 of SEQ ID No. 1 [2].

46. (Amended) An *in vitro* process of using binding entities having the capability of binding specifically to an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4 [2], or an integrin heterodimer comprising said subunit α10 and a subunit or to homoloques or fragments thereof having essentially the same biological activity, as markers or target molecules of cells or tissues expressing said integrin subunit α10, which cells or tissues are of animal including human origin.

48. (Amended) An *in vitro* process according to claim 46, whereby said fragment is a peptide comprising the amino acid sequence SEQ ID No.: 7 [KLGFFAHKKKREEKLEQ].

49. (Amended) An *in vitro* process according to claim 46, were said fragment comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID no. 2[1].

50. (Amended) An *in vitro* process according to claim 46, whereby said fragment comprises the amino acid sequence from about amino acid no. 140 to about amino acid No. 337 of SEQ ID No. 2 [1].

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52. (Twice Amended) An *in vitro* process according to any one of claims 46-51, which is a process for detecting the presence of an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4[2] or of an integrin heterodimer comprising said subunit α10 and a subunit β, or of homologues or fragments thereof having essentially the same biological activity.

54. (Amended) An *in vitro* process for detecting the presence of a integrin subunit α10, or of a homologue or fragment of said integrin subunit having essentially the same biological activity, on cells, whereby a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID No. 2 [1] is used as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit al.

57. (Amended) An *in vitro* process according to claim 54, whereby said fragment peptide comprising the amino acid sequence [KLGFFAHKKIPEEEKREEKLEQ] SEQ ID No. 7.

58. (Amended) An *in vitro* process according to claim 54, whereby said fragment comprises the amino acid sequence from about amino acid No. 952 to about amino acid no. 986 of SEQ. ID, No. 2 [1].

64. (Amended) An *in vitro* process for determining the differentiation-state of cells during development, in pathological conditions, in tissue regeneration and in therapeutic and physiological reparation of cartilage, whereby a polynucleotide or oligonucleotide chosen from the nucleotide sequence shown in SEQ ID No. 2 [1] is used as

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a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit α10.

66. (Amended) An *in vitro* process according to claim 65, whereby said polynucleotide or oligonucleotide is a polynucleotide or oligonucleotide coding for a peptide comprising the amino acid sequence [KLGFFAHKKIPEEEKREEKLEQ] SEQ ID No. 7.

67. (Amended) An *in vitro* process according to claim 65, whereby said peptide comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SDQ ID No. 2 [1].

68. (Amended) An *in vitro* process according to claim 65, whereby said peptide comprises the amino acid sequence from about amino acid no. 140 to about amino acid no. 337 of SEQ ID No. 2[1].

78. (Amended) An *in vitro* method of using binding entities having the capability of binding specifically to an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4 [2], or an integrin heterodimer comprising said subunit α10 and a subunit β or to homoloques or fragments thereof having essentially the same biological activity, for promoting adhesion of chondrocytes and/or osteoblasts to surfaces of implants to stimulate osseointegration.

86. (Amended) A process of using a collagen binding integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4 [2], or an integrin heterodimer comprising said subunit α10 and a subunit β, or a homologue or

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fragment of said integrin or subunit having essentially the same biologically activity, as a marker or target molecule of cells or tissues expressing said integrin subunit α10, which cells or tissues are of animal including human origin.

88. (Amended) A process according to claim 86, whereby said fragment is a peptide comprising the amino acid sequence [KLGFFAHKKIPEEEKREEKLEQ] SEQ ID No.: 7.

89. (Amended) A process according to claim 86, whereby said fragment comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID No. 2 [1].

90. (Amended) A process according to claim 86, whereby said fragment comprises the amino acid sequence from about amino acid no. 140 to about amino acid no. 337 of SEQ ID No. 2[1].

99. (Amended) A process of using binding entities having the capability of binding specifically to an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No., 2 [1] or SEQ ID No. 4 [2], or an integrin heterodimer comprising said subunit α10 and a subunit β, or to homoloques or fragments thereof having essentially the same activity, as markers or target molecules of cells or tissues expressing said integrin subunit α10, which cells or tissues are of animal including human origin.

101. (Amended) A process according to claim 99, whereby said fragment is a peptide comprising the amino acid sequence [KLGFFAHKKIPEEEKREEKLEQ] SEQ ID No. 7.

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102. (Amended) A process according to claim 99, whereby said fragment comprises the amino acid sequence from about amino acid no. 952 to about amino acid no. 986 of SEQ ID No. 2 [1].

103. (Amended) A process according to claim 99, whereby said fragment comprises the amino acid sequence from about amino acid no. 140 to about amino acid No. 337 of SEQ ID No. 2 [1].

105. (Twice Amended) A process according to any one of claims 99-104 which is a process for detecting the presence of an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 2 [1] or SEQ ID No. 4 [2], or of an integrin heterodimer comprising said subunit α10 and a subunit β, or of homoloques or fragments thereof having essentially the same biologically activity.

107. (Amended) A process for detecting the presence of an int r. subunit α10, or of a homologue or fragment of said integrin subunit having essentially the same activity, on cells, whereby a polynucleotide or oligonucleotide chosen from the group comprising a polynucleotide or oligonucleotide shown in SEQ ID No. 2 [1] is used as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit α1.

110. (Amended) A process according to claim 107, whereby said fragment is a peptide comprising the amino acid sequence [KLGFFAHKKIPEEEKREEKLEQ] SEQ ID No. 7.

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111. (Amended) A process according to claim 107, whereby said fragment comprises the amino acid sequence from about amino acid No. 952 to about amino acid no. 986 of SEQ ID No. 2 [1].

112. (Amended) A process according to claim 107, whereby said fragment comprises the amino acid sequence from about amino acid No. 140 to about amino acid No. 337 of SEQ ID No. 2 [1].

117. (Amended) A process for determining the differentiation-state of cells during development, in pathological conditions, in tissue regeneration and in therapeutic and physiological reparation of cartilage, whereby a polynucleotide or oligonucleotide chosen from the nucleotide sequence shown in SEQ ID No. 2 [1] used as a marker under hybridisation conditions wherein said polynucleotide or oligonucleotide fails to hybridise to a DNA or RNA encoding an integrin subunit $\alpha 10$.

119. (Amended) A process according to claim 117, whereby said polynucleotide or oligonucleotide is a polynucleotide or oligonucleotide coding for a peptide comprising the amino c acid-sequence SEQ ID No. 7 [KLGFFAHKKIPEEKREEKLEQ].

120. (Amended) A process according to claim 117, whereby said polynucleotide or oligonucleotide is a polynucleotide or oligonucleotide coding for a peptide comprising the amino acid sequence from about amino acid no. 952 to about amino. 986 of SEQ ID No. 2 [1].

121. (Amended) A process according to claim 117, whereby said polynucleotide or oligonucleotide is a polynucleotide or oligonucleotide coding for a peptide comprising

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the amino acid sequence from about amino acid no. 140 to about amino acid no. 337 of DEQ ID No. 2 [1].

127. (Amended) A method of using binding entities having the capability of binding specifically to an integrin subunit α10 comprising the amino acid sequence shown in SEQ ID No. 2[1] or SEQ ID No. 4[2], or an integrin heterodimer comprising said subunit α10 and a subunit β, or to homologues or fragments thereof having essentially the same biological activity, for promoting adhesion of chondrocytes and/or osteoblasts to surfaces of implants to stimulate osseointegration.